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# Screening, diagnosis and treatment of iron deficiency in chronic heart failure: putting the 2016 European Society of Cardiology heart failure guidelines into clinical practice

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Iron deficiency is common in patients with chronic heart failure (CHF) and is associated with reduced exercise performance, impaired health-related quality of life and an increased risk of mortality, irrespective of whether or not anaemia is present. Iron deficiency is a serious but treatable condition. Several randomized controlled clinical trials have demonstrated the ability of intravenous (IV) iron, primarily IV ferric carboxymaltose (FCM), to correct iron deficiency in patients with heart failure with reduced ejection fraction (HFrEF), resulting in improvements in exercise performance, CHF symptoms and health-related quality of life. The importance of addressing the issue of iron deficiency in patients with CHF is reflected in the 2016 European Society of Cardiology (ESC) heart failure guidelines, which recognize iron deficiency as an important co-morbidity, independent of anaemia. These guidelines recommend that all newly diagnosed heart failure patients are routinely tested for iron deficiency and that IV FCM should be considered as a treatment option in symptomatic patients with HFrEF and iron deficiency (serum ferritin < 100 µg/L, or ferritin 100–299 µg/L and transferrin saturation < 20%). Despite these specific recommendations, there is still a lack of practical, easy-to-follow advice on how to diagnose and treat iron deficiency in clinical practice. This article is intended to complement the current 2016 ESC heart failure guidelines by providing practical guidance to all health care professionals relating to the procedures for screening, diagnosis and treatment of iron deficiency in patients with CHF.

## Keywords

Chronic heart failure • European Society of Cardiology • Iron deficiency • Guidelines • Ferric carboxymaltose

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## Iron deficiency in heart failure is common, important and treatable

Iron deficiency is a common co-morbidity in patients with chronic heart failure (CHF) and can exist with or without anaemia.<sup>1</sup> As many as ~40–70% of patients with CHF are iron-deficient.<sup>2–7</sup> Iron deficiency can be described as being either 'absolute' or 'functional'.<sup>8</sup> Absolute iron deficiency is the result of reduced iron stores [haemoglobin (Hb) and ferritin, present mainly in the liver, spleen and bone marrow].<sup>9</sup> In patients with CHF, iron stores may be depleted by malabsorption, malnutrition, and gastrointestinal blood loss (may be caused or exacerbated by the use of anticoagulants, antithrombotics, or non-steroidal anti-inflammatory drugs).<sup>9</sup> Functional iron deficiency is a result of impaired iron mobilization from storage sites. Patients with CHF usually have systemic chronic inflammation and elevated inflammatory cytokines, which increase hepcidin production by the liver. Hepcidin blocks iron absorption from the gastrointestinal tract and also iron mobilization from storage sites, including the reticuloendothelial system.<sup>9–11</sup> In addition, existing co-morbidities (e.g. renal dysfunction) and/or dietary restrictions (e.g. meat-free diet) may contribute further to the development of iron deficiency in patients with CHF.<sup>12</sup>

The physiological impact of iron deficiency extends beyond impairment of erythropoiesis and the associated risk of anaemia. Non-haematopoietic tissues, including skeletal and cardiac muscle, are dependent on iron as the key constituent of proteins involved in vital cellular processes, such as oxygen storage (as the component of myoglobin) and oxidative energy metabolism (as a component of oxidative enzymes and mitochondrial respiratory chain proteins).<sup>13,14</sup> Clinical studies in patients with CHF show that iron deficiency is associated with decreased exercise performance,<sup>4,15–17</sup> impaired health-related quality of life (QoL)<sup>18,19</sup> and an increased risk of morbidity<sup>20</sup> and mortality,<sup>2,4,21</sup> irrespective of the presence of anaemia.

Iron deficiency is a treatable condition. Data from randomized clinical trials performed in patients with heart failure with reduced ejection fraction (HFrEF) and iron deficiency have demonstrated improvements in exercise capacity and QoL, and a reduction in hospitalizations following treatment with intravenous (IV) iron.<sup>22–26</sup>

The clinical benefit of treating iron deficiency in patients with CHF is reflected in the latest 2016 European Society of Cardiology (ESC) guidelines for heart failure (HF), in which iron deficiency is recognized as an important co-morbidity, independent of anaemia, and specific recommendations relating to its diagnosis and treatment are provided.<sup>1</sup>

Despite these guideline recommendations, iron deficiency is still under-diagnosed and under-treated in clinical practice.<sup>27,28</sup> Therefore, many patients are being denied therapy that may potentially have a positive impact on both cardiovascular function and QoL. This may be partially due to the lack of practical advice on how to screen, diagnose and treat iron deficiency. In recognition of the lack of practical recommendations, a global working group of physicians with expertise in this field decided to address this clinical need. This article is intended to complement the 2016 ESC HF guidelines by providing practical guidance for all health care professionals (HCPs) worldwide who are involved in the management of patients with

HF and are, therefore, in a position to identify and/or treat iron deficiency.

## Development of practical recommendations

Practical recommendations complementing ESC guidelines have previously been developed for the management of other treatments in CHF (e.g. angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers).<sup>29,30</sup> The practical recommendations outlined in this manuscript were developed, discussed and agreed by the authors during a series of working group meetings that took place in 2016 and 2017. This practical guidance addresses the management of patients with iron deficiency in a stepwise manner, from initial screening and diagnosis through to treatment and follow-up.

## Practical recommendations on the screening and diagnosis of iron deficiency in patients with heart failure

The current 2016 ESC HF guidelines<sup>1</sup> recommend that evaluation of iron status should be considered in the diagnostic work-up of all newly diagnosed HF patients (class of recommendation I, level of evidence C). A practical recommendation of the working group is that iron status should also be evaluated in patients with existing CHF, particularly if they are symptomatic despite receiving optimal background HF medications. In addition, as part of routine follow-up, consideration should be given to the re-evaluation of iron status 1–2 times per year, as well as after hospitalization for HF.

Ferritin and transferrin saturation (TSAT) are widely available blood markers for evaluating iron status. Their use for the diagnosis of iron deficiency is recommended by the 2016 ESC HF guidelines.<sup>1</sup> Ferritin is an intracellular iron-storage protein secreted by iron-storing tissues (e.g. liver and reticuloendothelial system). Serum ferritin concentrations are a surrogate marker of stored iron quantity.<sup>9</sup> TSAT (defined as % of transferrin that has iron bound to it) is used as a marker of the availability of circulating iron to supply metabolizing cells.<sup>9</sup> TSAT value is calculated by dividing the serum iron concentration by the total iron-binding capacity (TIBC):

$$\text{TSAT (\%)} = \frac{\text{Serum iron (\mu g/dL)}}{\text{TIBC (\mu g/dL)}} \times 100$$

The 2016 ESC HF guidelines recommend treating iron deficiency based on a serum ferritin level < 100 µg/L, or 100–299 µg/L when TSAT < 20%. Two different cut-offs are used because ferritin levels may become elevated in the presence of inflammation and may, therefore, appear to be within the normal range (100–300 µg/L). As ferritin, an acute-phase protein, is elevated as a result of inflammation, TSAT levels < 20% indicate that insufficient circulating iron is available to supply metabolizing cells (functional iron deficiency).<sup>9</sup> Therefore, in accordance with the 2016 ESC HF guidelines, it is

important to ensure that both ferritin and TSAT testing is performed simultaneously and evaluated together when assessing iron status (Figure 1). Lower ferritin cut-offs (e.g.  $<30 \mu\text{g/L}$ ) may be used to confirm the presence of iron deficiency in other disease settings and are often displayed on laboratory test results as the lower limit of normal. However, the thresholds defined above are recommended to diagnose iron deficiency in patients with CHF.

Note that mean corpuscular volume, mean corpuscular Hb (MCH) and MCH concentration have been found to be unreliable markers of iron deficiency status.<sup>31</sup> Measuring their levels is not recommended for assessment of iron deficiency in patients with HF. In addition, serum iron concentrations can vary substantially between HF patients, and also exhibit large diurnal variations and, therefore, serum iron alone should not be used as a marker of iron status.<sup>32</sup> Ferritin and TSAT should be used instead.

In patients who are both iron-deficient and anaemic, it is important to investigate the underlying causes of reduced Hb levels and to exclude other pathologies, including occult blood loss. Measurement of Hb levels is important as this has implications for IV iron dosing (discussed in the next section).

## Practical recommendations on the treatment of iron deficiency in patients with chronic heart failure

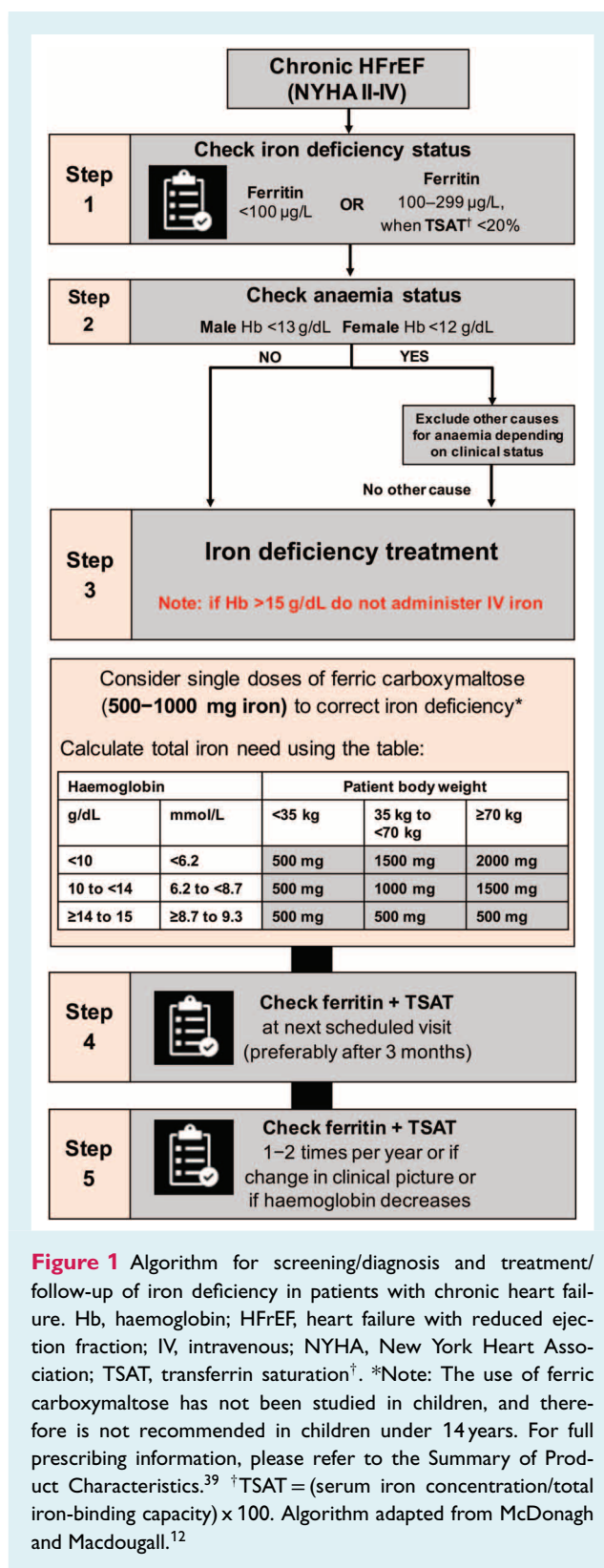
The current treatment options for the correction of iron deficiency in the general population consist of IV or oral iron. The 2016 ESC HF guidelines specifically recommend that, in patients with symptomatic HF (HFrEF), iron deficiency is treated with IV ferric carboxymaltose (FCM).<sup>1</sup> This recommendation is based on clinical trial evidence demonstrating the benefit of IV FCM therapy in this patient population. In turn, oral iron therapy has been found to be ineffective for replenishment of iron stores and improvement of clinical status in patients with CHF (further details below).<sup>33</sup>

### Intravenous iron therapy

Of the IV iron preparations licensed for therapeutic use, IV FCM has been most extensively studied for the treatment of iron deficiency in patients with HFrEF. The efficacy of FCM has been evaluated in several randomized clinical trials, including FAIR-HF,<sup>22</sup> CONFIRM-HF<sup>24</sup> and EFFECT-HF,<sup>34</sup> which enrolled symptomatic patients with stable CHF [left ventricular ejection fraction (LVEF)  $\leq 45\%$ ] and iron deficiency (Table 1).

The FAIR-HF study found that, compared with placebo, FCM therapy was associated with significant improvements in patient self-reported QoL (measured using patient self-reported global assessment) and HF symptoms [measured by New York Heart Association (NYHA) class] over a 6-month period, irrespective of anaemia status.

The CONFIRM-HF study followed patients for 52 weeks. The primary endpoint — demonstrating that FCM therapy was associated with significant improvements in exercise capacity (assessed



**Figure 1** Algorithm for screening/diagnosis and treatment/follow-up of iron deficiency in patients with chronic heart failure. Hb, haemoglobin; HFrEF, heart failure with reduced ejection fraction; IV, intravenous; NYHA, New York Heart Association; TSAT, transferrin saturation<sup>†</sup>. \*Note: The use of ferric carboxymaltose has not been studied in children, and therefore is not recommended in children under 14 years. For full prescribing information, please refer to the Summary of Product Characteristics.<sup>39</sup> <sup>†</sup>TSAT = (serum iron concentration/total iron-binding capacity)  $\times 100$ . Algorithm adapted from McDonagh and Macdougall.<sup>12</sup>

using the 6-minute walk test) after 24 weeks — was met. A secondary endpoint analysis found that FCM also reduced the risk of hospitalization in patients with CHF, compared with placebo.

**Table 1** Design and dosing regimens used in the FAIR-HF, CONFIRM-HF and EFFECT-HF studies

Study	Study design and duration	No. of patients treated	Key inclusion criteria	Dosing regimen	Single dose of iron used	Administration method	Mean total iron dose	Total no. of injections in FCM group
FAIR-HF (Anker <i>et al.</i> ) <sup>22</sup>	Double-blind, placebo-controlled, randomized; 24 weeks	FCM: 304 Placebo: 155	NYHA class II (LVEF $\leq 40\%$ ) or III (LVEF $\leq 45\%$ ) Hb 9.5–13.5 g/dL Ferritin $< 100 \mu\text{g/L}$ or 100–299 $\mu\text{g/L}$ + TSAT $< 20\%$	Dose calculated according to Ganzoni formula FCM 200 mg iron/week until iron repletion (correction phase) then every 4 weeks during maintenance phase	100 mg or 200 mg	Bolus injection	1850 mg	Median 6 (3–7) in the correction phase
CONFIRM-HF (Ponikowski <i>et al.</i> ) <sup>24</sup>	Double-blind, placebo-controlled, randomized; 52 weeks	FCM: 150 Placebo: 151	NYHA class II/III (LVEF $\leq 45\%$ ) Hb $< 15 \text{ g/dL}$ Ferritin $< 100 \mu\text{g/L}$ or 100–300 $\mu\text{g/L}$ + TSAT $< 20\%$	FCM 500–2000 mg iron in therapy phase (baseline and week 6); 500 mg iron as maintenance (weeks 12, 24, 36) if iron deficiency still present	500 mg or 1000 mg	Bolus injection	1500 mg	$> 75\%$ of patients receiving FCM required a maximum of 2 injections to achieve iron repletion during the study
EFFECT-HF (van Veldhuisen <i>et al.</i> ) <sup>34</sup>	Open-label, standard of care-controlled, randomized; 24 weeks	FCM: 86 Standard of care: 86	NYHA class II/III (LVEF $\leq 45\%$ ) Hb $< 15 \text{ g/dL}$ Ferritin $< 100 \mu\text{g/L}$ or 100–300 $\mu\text{g/L}$ + TSAT $< 20\%$ Peak $\text{VO}_2$ 10–20 mL/kg/min (reproducible)	FCM 500–2000 mg iron in therapy phase (baseline and week 6); 500 mg iron as maintenance (week 12) if iron deficiency still present	500 mg or 1000 mg	Bolus injection or infusion	1204 mg	96% of patients received a maximum of 2 injections

FCM, ferric carboxymaltose; Hb, haemoglobin; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; TSAT, transferrin saturation;  $\text{VO}_2$ , oxygen uptake.†TSAT = (serum iron concentration/total iron-binding capacity)  $\times 100$ .



The open-label, randomized EFFECT-HF study evaluated the impact of FCM vs. standard of care on exercise capacity [assessed by change in peak oxygen uptake ( $\text{VO}_2$ ) to week 24] in 174 patients with stable CHF and iron deficiency. After 24 weeks, FCM treatment was associated with a significantly beneficial effect on peak  $\text{VO}_2$ , vs. standard of care, in the primary analysis. This was observed in both anaemic and non-anaemic patients.<sup>34</sup>

Based on the data from FAIR-HF,<sup>22</sup> CONFIRM-HF<sup>24</sup> and a meta-analysis of randomized clinical trials<sup>26</sup> that evaluated the impact of IV iron therapy in patients with HFrEF, the current 2016 ESC HF guidelines recommend the use of IV FCM for the treatment of iron deficiency in CHF (class of recommendation IIa, level of evidence A). Furthermore, a recent meta-analysis of individual patient data has demonstrated a reduction in recurrent cardiovascular hospitalizations and cardiovascular mortality with IV FCM in systolic HF patients with iron deficiency.<sup>35</sup> The subsequent sections will provide some practical guidance relating to the use of IV FCM for the treatment of iron deficiency in patients with CHF.

## Oral iron

Oral iron therapy is frequently used as a first-line treatment in the correction of iron deficiency in patients with CHF. However, there is a lack of clinical data supporting its efficacy for use in this setting.

A recent randomized, placebo-controlled clinical trial (IRONOUT HF) evaluated the impact of high-dose oral iron polysaccharide on exercise capacity (assessed by change in peak  $\text{VO}_2$  from baseline to week 16) and HF symptom improvement in patients with HFrEF and iron deficiency.<sup>33</sup> The study found that oral iron minimally replenished iron stores in this patient population, compared with placebo, and did not improve exercise capacity or HF symptoms. The results of the IRONOUT HF study do not support the use of oral iron therapy for the correction of iron deficiency in patients with HFrEF. There have been no randomized controlled trials where IV iron has been compared directly with oral iron in patients with CHF.

Furthermore, oral iron is poorly tolerated in patients with CHF, with gastrointestinal side effects occurring in up to 60% of patients.<sup>12</sup> The low rate of iron absorption from oral iron preparations means that they are less rapidly effective than IV iron, and therefore a relatively long duration of oral iron therapy (in some cases >6 months) may be required to achieve iron repletion.<sup>12</sup>

## Which patients are suitable candidates for intravenous iron?

The FAIR-HF, CONFIRM-HF and EFFECT-HF studies enrolled CHF patients with  $\text{LVEF} \leq 45\%$ , and demonstrated the efficacy of IV FCM with respect to improving functional capacity, HF symptoms and health-related QoL,<sup>22,24,34</sup> while potentially reducing risk of HF-related hospitalizations in this patient population.<sup>24</sup> These clinical trials were not designed for, or powered to, evaluate the effect of treatment on survival. Therefore, the potential efficacy of IV iron therapy in reducing mortality in CHF patients has not been demonstrated to date. The efficacy and safety of IV

iron therapy has not yet been established in acute HF, or in HF with preserved ejection fraction (HFpEF, defined as  $\text{LVEF} \geq 50\%$ ). These gaps in knowledge are being addressed in ongoing clinical trials.<sup>36–38</sup>

Contraindications for the use of FCM in patients with CHF and iron deficiency are few and include: hypersensitivity to the active substance, to FCM, or any of its excipients; known serious hypersensitivity to other parenteral iron products; the presence of anaemia not attributed to iron deficiency (e.g. other microcytic anaemia); evidence of iron overload; or disturbances in the utilization of iron<sup>39</sup> (Table 2).

It is also important to note that the efficacy and safety of IV FCM have not been evaluated in patients with Hb levels >15 g/dL, and therefore the drug should not be used in this patient population. Furthermore, IV iron should be used with caution in patients with acute or chronic infection according to the opinion of the treating physician, and treatment with IV FCM should be stopped in patients with ongoing bacteraemia.<sup>39</sup>

## Who can administer intravenous ferric carboxymaltose therapy?

A range of HCPs, including the general practitioner, nurse and hospital physician, can administer IV FCM therapy. In clinical practice, this varies between treatment centre and country based on local prescribing regulations or laws. FCM can be administered in any health care setting where staff are trained and equipment is available to evaluate and treat a potential hypersensitivity reaction. The risk of hypersensitivity reactions with IV FCM is low, with a frequency (events/patients treated) of  $\geq 0.1\%$  to <1.0% observed during clinical trials and post-marketing surveillance.<sup>39</sup> This is in contrast to the historical risk of older IV iron preparations (e.g. iron dextran), for which an increased risk of anaphylaxis has been observed.<sup>40</sup>

## How to administer and monitor intravenous ferric carboxymaltose therapy?

Ferric carboxymaltose contains 50 mg iron/mL. A 2 mL ampoule contains 100 mg of iron and a 10 mL ampoule contains 500 mg of iron. The determination of the initial iron need is calculated based on body weight and Hb levels, rather than ferritin or TSAT levels (used to diagnose the presence of iron deficiency) (Figure 1). The maximum recommended cumulative dose of FCM is 1000 mg iron (20 mL FCM)/week.

Intravenous FCM can be given as an injection or infusion. It is easily administered as an undiluted slow bolus injection (100 mg/min, or 15 min for a 1000 mg dose). Note that if administered as an IV infusion, FCM should not be over-diluted as this affects the stability of the drug. A dilution plan of FCM for IV infusion is displayed in Table 3. Patients should be observed for adverse effects for at least 30 min following each IV injection.

After IV administration of the correction dose, we recommend that iron status be re-evaluated at 3 months. Early re-evaluation of

**Table 2** Practical guidance on the treatment of iron deficiency in patients with chronic heart failure**Why screen for iron deficiency?**

1. Iron deficiency is common in CHF and is associated with reduced functional capacity, impaired quality of life and a worse prognosis, irrespective of anaemia status
2. Clinical trials of IV iron therapy conducted in patients with symptomatic HFrEF demonstrate that correction of iron deficiency is associated with significant improvements in exercise capacity, symptoms, health-related quality of life, and possible reductions in recurrent hospitalizations

**In whom and when to give IV iron therapy?***Indications*

1. IV FCM should be considered in symptomatic patients with chronic systolic HFrEF (LVEF <40%) and iron deficiency (class of recommendation IIa, level of evidence A)
2. Iron deficiency can be diagnosed based on the following cut-offs: serum ferritin <100 µg/L, or serum ferritin 100–299 µg/L when TSAT<sup>†</sup> <20%

*Contraindications*

1. Hypersensitivity to the active substance, to FCM, or any of its excipients
2. Known serious hypersensitivity to other parenteral iron products
3. Anaemia not attributed to iron deficiency, e.g. other microcytic anaemia
4. Evidence of iron overload or disturbances in the utilization of iron

*Cautions/seek specialist advice*

1. Use with caution in patients with acute or chronic infection; treatment with FCM should be stopped in patients with ongoing bacteraemia
2. Patients with known drug allergies, including those with a history of severe asthma, eczema or other atopic allergies, may be at an increased risk of hypersensitivity reaction
3. Increased risk of hypersensitivity reactions to parenteral iron complexes in patients with immune or inflammatory conditions (e.g. systemic lupus erythematosus and rheumatoid arthritis)
4. No clinical evidence for IV FCM in patients with HFpEF (LVEF ≥ 50%) and limited clinical evidence in HFmrEF (LVEF 40–49%)
5. The efficacy and safety of IV FCM has not been evaluated in patients with Hb level > 15 g/dL

**Which iron preparation/route?**

1. IV iron therapy with FCM is recommended by the current 2016 ESC HF guidelines (class of recommendation IIa, level of evidence A)
2. Oral iron therapy has not been shown to be an effective treatment option for iron deficiency in patients with CHF

**How should IV iron be administered?**

1. Determination of the initial iron need is calculated based on body weight and Hb levels (see dosing table in Figure 1)
2. FCM may be given intravenously as an undiluted slow bolus injection, or an infusion that requires dilution. If given as infusion, it should not be over-diluted (see dilution plan in Table 3)
3. The maximum recommended cumulative dose of FCM is 1000 mg of iron (20 mL FCM)/week
4. Patients should be observed for adverse effects for at least 30 min following each IV injection

**Where to perform the treatment?**

1. IV FCM can be administered in the hospital or community setting, where staff are trained and equipped to monitor for and manage hypersensitivity reactions

**Monitoring of iron status**

1. Following replacement, iron status should be re-evaluated in 3 months and further iron repletion provided as needed, as well as evaluation for blood loss as indicated
2. Early re-evaluation of iron status (i.e. within 4 weeks of IV iron administration) should be avoided as ferritin levels increase markedly following IV iron administration, and cannot be used as an indicator of iron status during this time
3. Consider evaluating iron status as part of routine practice in patients with known CHF (1–2 times per year) or when symptoms remain despite receiving optimal background HF medications

CHF, chronic heart failure; ESC, European Society of Cardiology; FCM, ferric carboxymaltose; Hb, haemoglobin; HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IV, intravenous; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; TSAT, transferrin saturation<sup>†</sup>.

<sup>†</sup>TSAT = (serum iron concentration/total iron-binding capacity) × 100.

**Table 3** Dilution plan for ferric carboxymaltose for intravenous infusion

Equivalent iron dose to be repleted	Volume of FCM required	Maximum amount of sterile 0.9% m/V sodium chloride solution	Minimum administration time
500 mg	10 mL	100 mL	6 min
1000 mg	20 mL	250 mL	15 min

FCM, ferric carboxymaltose; m/V, mass/volume %.

iron status (i.e. within 4 weeks of IV iron administration) should be avoided as serum levels of ferritin can increase markedly following administration of IV iron and cannot be utilized as a marker of iron status during this time.

Further iron repletion should be provided as needed. If there is no response or Hb levels decrease, further investigation for other underlying causes should be considered as clinically indicated, particularly occult blood loss. After correction of iron deficiency, as part of routine follow-up consider re-evaluation of iron parameters (ferritin and TSAT) 1–2 times per year. Iron status should be re-evaluated if patients remain symptomatic despite receiving optimal background HF medications, or in the event that Hb levels decrease (Figure 1).

Clinical studies have demonstrated that IV FCM is well tolerated with an acceptable safety profile in patients with CHF.<sup>22,24</sup> The most common side effects (occurring at a frequency of  $\geq 1.0\%$  to  $< 10.0\%$ ) reported during clinical trials and post-marketing surveillance include dizziness, headache, hypertension, hypophosphataemia, injection-site reactions, and nausea.<sup>39</sup> In patients who are iron-deficient and anaemic, appropriate investigation to determine the underlying cause of anaemia and to exclude other pathologies based on local clinical practice guidelines should be implemented as a safety measure. The risk of hypersensitivity reactions with IV FCM is low, with a frequency (events/patients treated) of  $\geq 0.1\%$  to  $< 1.0\%$  observed during clinical trials and post-marketing surveillance. Skin staining (or discolouration) can occur at the infusion site if there is extravasation of IV iron.<sup>39</sup> This may be avoided by ensuring best practice in IV line placement and care. In case of paravenous leakage, the administration of FCM must be stopped immediately.<sup>39</sup>

## Conclusions

There is evidence from randomized clinical trials to show that correction of iron deficiency with IV iron therapy in patients with CHF (LVEF  $\leq 45\%$ ) provides improvements in functional capacity, HF symptoms and health-related QoL, and may reduce the risk of HF-related hospitalizations.<sup>22,24,34</sup>

The 2016 ESC HF guidelines recommend that iron status should be evaluated as part of the initial work-up of all newly diagnosed HF patients.<sup>1</sup> The working group also recommends that iron status is checked among patients with existing CHF independently of Hb level or when symptoms persist despite receiving optimal background HF medications.

Intravenous iron therapy with FCM is recommended by the 2016 ESC HF guidelines for the correction of iron deficiency, and should be considered in symptomatic patients with HFrEF and iron deficiency.<sup>1</sup>

## Knowledge gaps and areas for further research

It is important to note that, in the absence of certain clinical data, some of the practical recommendations made in this article are based on the collective expert opinion of the working group.

As outlined in the article, several knowledge gaps relating to the role of IV iron therapy in HF patients remain, many of which are being addressed by ongoing randomized clinical trials. These include the need for robust clinical data evaluating the impact of IV iron therapy on morbidity and mortality in systolic CHF patients with iron deficiency; these will be provided by the ongoing FAIR-HF2 (NCT03036462) and IRONMAN (NCT02642562) studies. Furthermore, the efficacy and safety of IV iron has not yet been established in patients with HFpEF or acute HF and iron deficiency — the ongoing FAIR-HFpEF (NCT03074591) and AFFIRM-AHF (NCT02937454) studies should provide a better insight into the role of IV iron therapy in each of these patient populations.

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